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**Docket # 2004Q-0151 Solae Company Qualified Health Claim re Soy Protein and Cancer**

Dear Dr. Shimakawa:

We are writing to protest the proposed “soy-protein-prevents-cancer” health claim and to request that the FDA hold a public hearing on this matter.

We dispute the claim made by Solae that its data is “based on the totality of publicly available scientific evidence” and hold that numerous experts qualified by scientific training and experience – including scientists from the FDA’s National Laboratory for Toxicological Research and the British Committee on Toxicity – have warned that soy protein can contribute to, accelerate the growth of and even cause cancer.

Numerous expert scientists have shown that soy protein poses well-documented risks to the thyroid gland and to the digestive, immune and neuro-endocrine systems of the body and that soy protein is one of the top eight allergens. Indeed, soy protein presents so many health risks to American consumers that products containing more than 6 grams of soy protein should carry a warning on the label, not a health claim. Because of these findings, the Weston A. Price Foundation will be submitting a petition to the FDA with regards to a warning label for soy protein.

In our June 14, 2004 and January 20, 2005 letters to the FDA we established that Solae was highly selective in its choice of studies and that it frequently misrepresented data and conclusions. We established the fact that a careful reading of the studies showed inconsistent, contradictory and inconclusive results that do not justify the conclusion that

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soy protein prevents cancer. In this document we have focused on studies that disprove the validity of the proposed health claim and that suggest the appropriateness of a warning label that would alert the American public to the possibility of increased cancer risk as a result of excessive soy protein consumption.

We maintain that the benefits cited by Solae are putative, not proven, and that the scientific community has longstanding concerns about soy protein's probable role in carcinogenesis and cancer growth. Until these concerns have been fully addressed, warning labels on soy protein are appropriate, not health claims. Therefore in the interest of public safety, we request that the FDA reject the Solae Company's proposed health claim and hold a public hearing on this matter.

Sincerely,

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## A. PRELIMINARY REQUIREMENTS

Solae proposes a health claim for soy protein products despite the fact that these soy products contain other naturally occurring antinutrients such as protease inhibitors (most notably trypsin inhibitors), phytates, lectins, oxalates and oligosaccharides, which may possess valuable pharmaceutical properties but which have also been linked in more than 100 studies to digestive distress, intestinal disorders, mineral deficiencies, flatulence and even cancer development and growth. Soy protein products also include phytoestrogens known as isoflavones, which are listed as "carcinogens" in the American

Chemical Society's 1976 textbook *Chemical Carcinogens* as well as other toxicology textbooks.

Furthermore, modern soy protein products – the chief beneficiaries of a health claim – include numerous toxins and carcinogens created during food processing, including nitrosamines, lysinoalanines, heterocyclic amines, furanones, chloropropanols, hexane and other solvents. These hazards were never properly acknowledged or addressed by Solae in its health claim petition or in its August 17, 2004 letter in response to comments submitted by the Weston A. Price Foundation. Indeed, Solae claimed that nitrosamines “are not present in soy foods.” This statement is untrue.

Nitrites, precursors to nitrosamines, have always been present in modern soy protein products, and the American public deserves to be properly warned about these carcinogens. In 1979, the Select Committee on Gras Substances (SCOGS) committee reported to the FDA that the amount of nitrites found in soy protein – either directly in soy food or indirectly from migration from the soy protein isolate used in packaging – was likely to be so small (50 parts per million) and that nitrosamines would not pose a health hazard to the public because the average person consumed no more than 150 mg per day of soy protein.<sup>1</sup> Today, people are consuming substantially greater amounts of soy protein. In addition to containing nitrites, soy protein isolates and other products that have undergone acid washes, flame drying or high temperature spray-drying processes contain preformed nitrosamines. In USDA studies undertaken in the 1980s, researchers found that soy protein isolate contained about twice the nitrite content found in other soy protein products, including overly toasted soy flour. They also found levels of 1.5 parts per billion of a potent nitrosamine known as N-nitrosodimethylamine (NDMA) in soy protein.<sup>2</sup> More recently, this highly volatile nitrosamine has been found in significant quantities in SPI.<sup>3</sup>

The California Environmental Protection Agency Office of Environmental Health Hazard Assessment has established safe levels for nitrosamines ranging from 40 ng per day for NDMA to 80 ug per day for the relatively weak nitrosamine N-nitrosodiphenylamine. According to Mike Fitzpatrick, Ph.D., a person who eats 100 grams of soy protein would exceed safe levels if NDMA is present in excess of 0.20 parts per billion in steam-treated soy flour or 0.36 parts per billion in soy protein isolate. The safe level of N-

nitrosdiphenylamine would be exceeded if present at levels in excess of 0.42 parts per million in steam-treated soy flour or 0.72 parts per million in soy protein isolate. Though very little information has been published on the levels of nitrosamines in soy products – and levels vary from batch to batch – this level of toxicity is not only possible but likely. Taking the USDA finding of 1.4 parts per billion, people eating 100 grams per day of soy protein – a goal promoted as healthful by Protein Technologies International (PTI) in their 1999 petition to the FDA and already consumed by some health-conscious Americans – could be exposed daily to *35 times* the safe limit of NDMA. Finally, Dr. Fitzpatrick notes that the safe levels are defined for a 70 kg adult male and that lower levels should be established for adult women, teenagers, children and infants.<sup>4</sup>

Solae also stated in its August 2004 rebuttal that “modern processing procedures eliminate the potential for lysinoalanine production.” This statement is also untrue, and the American public should be warned that soy protein may contain lysinoalanine, a cross-linked amino acid that is produced when the essential amino acid lysine is subjected to strong alkaline treatments. The modern food processing industry uses alkali to turn soybeans into soymilk, tofu, TSP, SPI, SPC and other products quickly and profitably. Only old-fashioned, fermented soy products or precipitated tofus made at home or in small, cottage-type industries can bill themselves as “lysinoalanine-free.”<sup>5,6</sup>

Ghulam Sarvar, Ph.D., of the Nutrition Research Division of the Banting Research Centre in Ottawa, writes: “The data suggested that LAL (lysinoalanine), an unnatural amino acid derivative formed during processing of foods, may produce adverse effects on growth, protein digestibility, protein quality and mineral bioavailability and utilization. The antinutritional effects of LAL may be more pronounced in sole-source foods such as infant formulas and formulated liquid diets, which have been reported to contain significant amounts (up to 2400 ppm of LAL in the protein) of LAL.”<sup>7</sup>

The highest levels of lysinoalanines are found in soy protein isolates manufactured using high alkaline solutions for use as sizing and coating adhesives for paper and paperboard products. Rats fed soy proteins processed using similar high-alkali baths have suffered kidney damage, specifically increased organ weights, lesions and kidney stones. The soy industry assures us that soy proteins intended for human consumption are safer because they are extracted at a pH level below 9.<sup>8-11</sup> A look at new processes receiving

patents today, however, reveals that the food processing industry has not made it a priority to keep alkaline levels low. For example, Kraft recently developed a process to "deflavor" soy milk, flour, concentrates and isolates by adjusting the pH to a level ranging from 9 to 12. This makes it possible to dissolve the soy proteins and release the "beany" flavors through a special ultrafiltrated membranous exhaust system.<sup>12</sup>

Other cross-linked amino acids, whose toxic effects are suspected, but not yet thoroughly researched, may also occur as a result of high alkali baths. Arginine, an important amino acid for proper growth, may be converted into the amino acid ornithine and from there into the problematic ornithinoalanine. Threonine produces methyl-dehydroalanine, which can undergo further reactions to form methyl-lysinoalanine and methyl-lanthionine. Cysteine can produce dehydroalanine and methyl-dehydroalanine.<sup>13-</sup>

<sup>15</sup> The American public should know that the research on the adverse effects that can be caused by lysinoalanines and other cross-linked amino acids is suggestive – though not yet conclusive – and that caution is advised.

Solae included in its claim of safety for soy protein the statement that the Bowman-Birk and Kunitz trypsin inhibitors in soybeans that have been linked to pancreatic cancer “are inactivated by heat applied during modern processing techniques.” This statement is only partially true.

Heat deactivates most – but not all – the protease inhibitors in soy. The only way to deactivate all of the protease inhibitors in soy is through the fermentation techniques used to make tempeh, miso and natto.<sup>16</sup> Otherwise some trypsin inhibitors *always* remain. The heat, pressure and chemical treatments used by modern food processors inactivate 80 to 90 percent of all the different protease inhibitors. At best, this 80 to 90 percent success rate is a promise, not a guarantee. The numbers of active protease inhibitors remaining in soy products vary from batch to batch, and investigators have found unexpectedly high levels of protease inhibitors present in some soy foods, and startlingly high levels in some soy formulas and soy protein concentrates.<sup>17-22</sup>

Accordingly, the American public also should be warned about the potential dangers from residual trypsin inhibitors found in modern soy protein products.

Levels of trypsin inhibitors are not only higher in GM soybeans but stubbornly resistant to deactivation by “toasting,” a heat treatment typically used by food processors.

Researchers performing safety tests for Monsanto found that the only way to eliminate sufficient numbers of the trypsin inhibitors was to toast the GM repeatedly, causing destruction of the most of the value of the soy protein as well. This and other evidence suggests that genetically modified soybeans are not “substantially equivalent” to conventional soybeans and that safety issues have not been properly addressed.<sup>23</sup> Yet soy foods made with both GM and regular soybeans would be eligible for the proposed health claim.

In its health claim petition Solae claimed that soy protein is “safe and lawful” yet conceded that soy protein isolate and other modern soy protein ingredients have never received GRAS (Generally Recognized as Safe) status as an additive to food. Soy isoflavones, the phytoestrogens present in all the soy protein products that reach the American marketplace, were denied GRAS status in 1999 when a petition submitted by Archer Daniels Midland for GRAS status was returned by CFSAN because of a failure to properly report adverse effects. Unlike most GRAS substances in use prior to 1958, soy protein isolate was not originally developed as a food but as an industrial product to bind and seal paper products. It therefore does not qualify as a product having a long history of safe use in the food supply. More seriously, as was mentioned above, soy protein isolate is known to include a number of toxins and carcinogens introduced by the high temperatures, high pressures and chemicals used in its manufacture.<sup>24-26</sup> In 1979, the Select Committee of GRAS Substances (SCOGS) examined safety issues pertaining to the manufacture of soy protein isolate and recommended that acceptable levels of the carcinogens nitrite and nitrosamines and the toxic amino acid lysinoalanine be established “to avoid future problems.”<sup>27</sup> To this date, safe levels have not been established and levels of these substances in edible food products are not closely monitored. The SCOGS committee determined that 150 mg per day of soy protein was the maximum safe dose, an amount far less than the 2.23 grams that are currently consumed by the average American, according to figures provided by the Solae Company in February 2004.<sup>28</sup>

The SCOGS committee’s recommendation of 150 mg of soy protein isolate per day as a “safe dose” is far lower than current per capita consumption. We maintain that

without a warning level, consumption of soy protein in America will continue to increase and that more and more food products will contain soy protein additives, both of which will present serious safety concerns including cancer risk to the public. The biggest risk is to people who are allergic to soy.

Soy is widely acknowledged as one of the top eight allergens, with one prominent researcher putting soy in the “top six” and another in the “top four.”<sup>29-34</sup> The increased soy protein in the food supply would not only be found in well-known soyfoods such as tofu, soy milk and veggie burgers – foods that allergy sufferers know enough to avoid – but also from soy proteins incorporated into the recipes for baked goods, canned, packaged and other processed foods. This “hidden” soy poses a danger to allergy sufferers, who may experience symptoms that range from mild to life-threatening, involving the gastrointestinal, cutaneous and respiratory systems. A recent Swedish study reported four fatalities as the result of soy protein hidden in foods such as hamburgers. Furthermore, allergy experts have warned that the increased use of soy protein in food products is increasing the potential for sensitization.<sup>35</sup>

Soy protein products should also contain a warning label because health claims (such as the current proposed, qualified health claim that “soy protein prevents cancer”) are encouraging many health-conscious consumers to increase their consumption of soy protein to 25 grams or more per day. People at special risk are vegetarians and vegans who choose soy as their main source of protein, individuals self medicating with soy protein products to try to prevent or reverse cancer and other diseases, and those at risk for or afflicted with thyroid disease. The Working Group of the British Committee on Toxicity (COT) recently “identified individuals with hypothyroidism as a subgroup of potential concern,” noting that a “soy-rich diet may provide sufficient concentrations of phytoestrogens to interfere with thyroxine replacement therapy.”<sup>36</sup> The FDA’s National Laboratory of Toxicological Research in Arkansas, has published research showing that “Isoflavones are inhibitors of thyroid peroxidase, which is an enzyme needed for the body to properly make the thyroid hormones T3 and T4. Inhibition can be expected to generate thyroid abnormalities, including goiter and autoimmune thyroiditis. There exists

a significant body of animal data that demonstrates goitrogenic and even carcinogenic effects of soy products.”<sup>37-40</sup>

Soy is especially risky for Americans taking thyroid drugs like Synthroid. Boosting the thyroid with drugs such as Synthroid, then depressing it with thyroid inhibitors like soy protein can put extreme stress on the thyroid. Environmental scientist Mike Fitzpatrick, PhD, points out that this is the classic way that researchers induce thyroid tumors in laboratory animals. One serving of soy food provides up to three times the goitrogenic potency of the pharmaceutical thyroid-inhibiting drugs methimazole and 6-propylthiouracil.<sup>41</sup> Accordingly, a health claim is inappropriate and a warning label is appropriate.

The American public is also entitled to know that increased soy isoflavones in the food supply would have a cumulative or exponential effect with other xenoestrogens in the environment. Toxicologists at the Centre for Toxicology, The School of Pharmacology at the University of London have stated that “estrogenic agents are able to act together to produce significant effects when combined at concentrations below their NOECs. . . Hazard assessments that ignore the possibility of joint action of estrogenic chemicals will almost certainly lead to significant underestimations of risk.”<sup>42</sup> Solae has failed to address this crucial matter in either its original petition or its August 17, 2004 letter in response to the Weston A. Price Foundation’s comments of June 14, 2004.

Solae argues that cancer statistics and epidemiological studies indicate striking geographical differences in cancer morbidity and mortality, with lower death rates from breast, prostate and gastrointestinal cancers in Asia than in the United States. While soy may be a factor in these reduced rates, other dietary and lifestyle factors are almost certainly involved. Certainly, there is no direct evidence for beneficial cancer-reducing effects of the phytoestrogens in soy protein foods. More importantly, we contend that if the petitioners attribute decreased rates of breast, prostate and colon cancer in Asia to soy consumption, then the same logic requires them to blame higher rates of cancer of the esophagus, stomach, thyroid, pancreas and liver in Asian countries to consumption of soy.<sup>43</sup> They have not done so.

Solae has also neglected to address the fact that the proper use of soy protein for cancer prevention requires sure knowledge of windows of vulnerability – or opportunity – as found in utero, during infancy, before puberty, during puberty, during the reproductive years and beyond. Solae’s promotion of the idea that soy protein is a “health food” has led to indiscriminate consumption of soy protein-containing foods by men, women and children, with no understanding of the fact that a substance that might be helpful in one stage of the life cycle could be harmful in another. Whether soy protein will prevent, contribute to, accelerate the growth of, or even cause cancer depends not only on biochemical individuality but on these windows of vulnerability.

Although research to date is inconsistent and contradictory, it leaves no doubt that the phytoestrogens in soy protein exert their influence throughout the body in many different ways and that they have the potential to exert adverse actions. Patricia L Whitten, Ph.D., of Emory University explains that “these potential roles fall into three major areas: 1) estrogen agonists whose activational actions could prove beneficial to postmenopausal women but might be harmful to the degree that they contribute to carcinogenesis or other adverse effects. 2) antiestrogens or antiproliferative agents that could help to prevent estrogen-dependent carcinoma by antagonizing estrogen action but could also contribute to infertility by suppressing normal reproductive function and 3) developmental toxins that could disrupt sexual differentiation by altering sex-specific patterns of development but might also provide protection against environmental estrogens by altering steroid response thresholds.”<sup>44</sup> We believe that the possible benefits of soy protein come with possible risks, including an increased risk of cancer, and that the American public deserves to be warned of these risks.

## B. SCIENTIFIC EVIDENCE

Solae states that “soy protein is a major source of dietary protein worldwide.” This statement is not true despite the fact that soy protein consumption has greatly increased worldwide as the result of intense marketing efforts by the soy industry and/or giveaways by government and charitable organizations. Soy foods have been a dietary

component in some Asian countries for centuries, not millennia, and are eaten there in small amounts as a condiment, not as a staple. Furthermore, the types of soy foods eaten traditionally in the countries of Asia are almost entirely whole soy foods prepared by fermentation and precipitation methods, not fractionated soy proteins produced by industrial food processing. This difference is highly significant in that modern processing methods used by the soy industry produce nitrosamines and other carcinogens. A recent study from the University of Illinois at Urbana-Champaign indicates that “highly processed soy may stimulate estrogen-dependent breast cancer.” According to William Helferich, MD, one of the study’s authors, “Soy has been correlated with low rates of breast cancer in Asian populations, but soy foods in Asia are made from minimally processed soybeans or defatted, toasted soy flour, which is quite different from soy products consumed in the U.S.” We include this important study below in our section on breast cancer.

## BREAST CANCER

Soy protein can cause the proliferation of breast cancer cells, increasing a woman’s risk of developing breast cancer and also posing special dangers to those already afflicted with breast cancer. The latter group includes not only women who have already been diagnosed with breast cancer, but those in the early stages prior to diagnosis. These people deserve to be warned about the fact that soy protein consumption could put them at serious risk.

We are not alone in this concern. The British government’s Committee on Toxicity (COT) writes in Chapter 15 -- Phytoestrogens and Cancer of its “Working Draft on Phytoestrogen” that “Short-term dietary supplementation has been shown to cause a proliferative response in premenopausal women with breast disease whereas a proliferative effect was not reported in premenopausal women without breast disease. However, phytoestrogen treatment did induce a weak estrogenic effect in these women as shown by modulation of the levels of the oestrogen responsive gene products apolipoprotein D and pS2 in nipple aspirate.” COT further states: “The animal data on breast cancer is conflicting. A number of studies have shown that genistein has a

protective effect in animal models of chemically induced cancer. However, similar experiments using tumour implant models showed that genistein stimulated the growth of implanted mammary tumours both by dietary and subcutaneous administration.” The full text of this report can be found at

<http://www.foodstandards.gov.uk/multimedia/webpage/phytoreportworddocs>

The following studies establish that soy protein (and its constituent isoflavones) have the potential to increase breast cancer risk and disease progression. Accordingly, a “soy-protein-prevents-cancer claim” would encourage women to eat foods that would, in fact, increase their risk. All quotations included below are from the original journal articles.

**Dees C, Foster JS et al.** Dietary estrogens stimulate human breast cells to enter the cell cycle. *Environ Health Perspect*, 1997, 105, 633-636.

“Genistein, a dietary estrogen, inhibits the growth of breast cancer cells at low doses but additional studies have suggested that genistein stimulates proliferation of breast cancer cells. . . Our findings are consistent with a conclusion that dietary estrogens do not act as anti-estrogens, but act like DDT and estradiol to stimulate breast cancer cells to enter the cell cycle. Women should not consume particular foods (soy derived products) to prevent breast cancer.”

**Martin PM, Horwitz KB et al.** Phytoestrogen interaction with estrogen receptors in human breast cancer cells. *Endocrinol*, 1978, 103, 5, 1860-1867.

“The interactions of phytoestrogens with estrogen receptors were studied in the human breast cancer cell line, MCF-7. The phytoestrogens are also biologically active; they can markedly enhance tumor cell proliferation. In sum, phytoestrogens interact with the estrogen receptors of human breast cancer cells in culture and, therefore, may affect estrogen-mediated events in these cells.”

**Allred CD, Ju YH et al.** Dietary genistein stimulates growth of estrogen-dependent breast cancer tumors similar to that observed with genistein. *Carcinogenesis*, 2001b, 22, 1667-1673.

“The estrogenic soy isoflavone, genistein, stimulates growth of estrogen-dependent human breast cancer (MCF-7) cells in vivo. Dietary genistein resulted in increased tumor growth, pS2 expression and cellular proliferation similar to that observed with genistein. The remaining mice were switched to diets free of genistein and genistein. When mice were placed on isoflavone-free diets, tumors regressed over a span of 9 weeks, metabolism of genistein to genistein occurred. . . . In summary, the glycoside genistein, like the aglycone genistein, can stimulate estrogen-dependent breast cancer cell growth in vivo. Removal of genistein or genistein from the diet caused tumors to regress.”

**Allred CD, Allred KF, et al.** Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose dependent manner. *Cancer Res*, 2001, 61, 13, 5045-5050.

“We have demonstrated that genistein stimulates growth of estrogen-dependent human breast cancer (MCF-7) cells in vivo (C.Y. Hsieh et al, *Cancer Res*, 58, 3833-3838, 1998). The isoflavones are a group of phytoestrogens that are present in high concentrations in soy. Soy protein diets containing varying amounts of genistein increased estrogen-dependent tumor growth in a dose dependent manner . . . Cell proliferation was greatest in tumors of animals given estrogen or dietary genistein (150 and 300 ppm). . . Here we present new information that soy protein isolates containing increasing concentrations of genistein stimulate the growth of estrogen-dependent breast cancer cells in vivo in a dose-dependent manner.

**Allred CD, Allred KF et al.** Dietary genistein results in larger MNU-induced, estrogen dependent mammary tumors following ovariectomy of Sprague-Dawley rats. *Carcinogenesis*, 2004, 25, 2, 211-218.

“The data suggest that in an endogenous estrogen environment similar to that of a postmenopausal woman, dietary genistein can stimulate the growth of a mammary carcinogen MNU-induced estrogen-dependent mammary tumours.”

**Allred CD, Allred KF et al.** Soy processing influences growth of estrogen-dependent breast cancer tumors in mice. *Carcinogenesis*, May 6, 2004.

“Soy-based products consumed in Asian countries are minimally processed whereas in the U.S. many of the soy foods and soy ingredients are highly processed. Soy foods contain complex mixtures of bioactive compounds which may interact with one another. The objective of this study was to evaluate the ability of various soy products containing genistein, the glycoside form of genistein to affect growth of MCF-7 cells transplanted into ovariectomized athymic mice. . . . Tumors in the negative control animals regressed throughout the study while tumors in the soy flour-fed animals remained basically the same size (neither grew nor regressed). In animals consuming soy molasses, Novasoy ®, mixed isoflavones or genistein alone tumor growth was stimulated when compared to animals consuming a control diet devoid of soy. These same dietary treatments resulted in increased cellular proliferation.”

**Hsich CY, Santell RC, et al.** Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells in vitro and in vivo. *Cancer Res*, 1998, 58, 3833-3838.

“Genistein, found in soy products, is a phytochemical with several biological activities. In the current study, our research focused on the estrogenic and proliferation-inducing activity of genistein. We have demonstrated that genistein enhanced the proliferation of estrogen-dependent human breast cancer (MCF-7) cells in vitro at concentrations as low as 10nM, with a concentration of 100nM achieving proliferative effects similar to those of 1 nM estradiol.”

**Ju YH, Doerge DR et al.** Dietary genistein negates the inhibitory effects of tamoxifen on growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice. *Cancer Res*, 2002, 1, 62, 9, 2474-2477.

“We investigated interactions between the soy isoflavone, genistein, and an antiestrogen, tamoxifen (TAM), on the growth of estrogen (E)-dependent breast cancer (MCF-7) cells. Dietary genistein negated/overwhelmed the inhibitory effect of TAM on

MCF-7 tumor growth, lowered E2 level in plasma and increased expression of E-responsive genes (e.g. pS2, PR, and cyclin D1). Therefore caution is warranted for postmenopausal women consuming dietary genistein while on TAM therapy for E-responsive breast cancer.”

**McMichael -Phillips DF, Harding C et al.** Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. *Am J Clin Nutr*, 1998, 68 (6 Suppl), 1431S-1435S.

This study examines the effects of dietary soy supplementation on the proliferation rate of premenopausal histologically normal breast epithelium and the expression of progesterone receptor. The proliferation rate of breast lobular epithelium significantly increased after 14d of soy supplementation when both the day of menstrual cycle and the age of patient were accounted for. . . Short-term dietary soy stimulates breast proliferation; further studies are required to determine whether this due to estrogen agonist activity and to examine the long-term effects of soy supplementation on the pituitary gland and breast.”

**de Lemos ML.** Effects of soy phytoestrogens genistein and daidzein on breast cancer growth. *Ann Pharmacother*, 2001, 35, 9, 1118-1121.

“OBJECTIVE: To determine whether genistein and daidzein, the major phytoestrogens in soy, can stimulate breast cancer growth. . . . CONCLUSIONS: Genistein and daidzein may stimulate existing breast tumor growth and antagonize the effects of tamoxifen. Women with current or past breast cancer should be aware of the risks of potential tumor growth when taking soy products.”

**Wang C, Kurzer MS.** Phytoestrogen concentration determines effects on DNA synthesis in human breast cancer cells. *Nutr Cancer*, 1997, 28, 3, 236-247.

“Our data suggest the possibility that, at typical concentrations in humans, phytoestrogens and related flavonoids and lignans may stimulate, rather than inhibit, growth of estrogen-dependent tumours. . . In conclusion, most of the phytoestrogens and related compounds tested in this study showed stimulation of DNA synthesis in estrogen-

dependent MCF-7 cells at low concentrations and inhibition of DNA synthesis in MCF-7 and estrogen-independent MDA-MB-231 cells at high concentrations. Although we observed inhibition at high levels, it is extremely important to consider that, at concentrations close to probable levels in humans, DNA synthesis was significantly induced in MCF-7 cells.”

**Ju YH, Allred CD et al.** Physiological concentrations of dietary genistein dose-dependently stimulate growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in athymic nude mice. *J Nutr*, 2001, 131, 11, 2957-2962.

“In conclusion, dietary treatment with genistein at physiological concentrations produces blood levels of genistein sufficient to stimulate estrogenic effects, as breast tumor growth, cellular proliferation and pS2 expression in athymic mice in a dose-responsive manner similar to that seen in vitro.”

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Phytoestrogens such as genistein found in soy protein products can cross the placenta, putting unborn children at risk. Accordingly, a health claim that encourages all Americans to eat more soy would endanger pregnant women and their unborn babies. Thus we propose a warning label for this at-risk population. We present here two studies indicating that perinatal exposure could increase the risk of babies later developing breast cancer.

**Hilakivi-Clark L, Cho E, Clark R.** Maternal exposure to genistein during pregnancy increases carcinogen-induced mammary tumorigenesis in female rat offspring. *Oncol Rep*, 1998, 5, 609-616.

“Human and animal data indicate that a high maternal estrogen exposure during pregnancy increases breast cancer risk among daughters. This may reflect an increase in the epithelial structures that are the sites for malignant transformation, i.e. terminal end buds (TEBs), and a reduction in epithelial differentiation in the mammary gland. Some

phytoestrogens, such as genistein, which is a major component in soy-based foods, . . . have estrogenic effects on the reproductive system, breast and brain. .. These findings indicate that maternal exposure to physiological doses of genistein mimics the effects of E2 on the mammary gland and reproductive systems in the offspring. Thus our results suggest that genistein acts as an estrogen in utero, and may increase the incidence of mammary tumors if given through a pregnant mother. “

**Yang J, Nakagama H et al.** Influence of perinatal genistein exposure on the development of MNU-induced mammary carcinoma in female Sprague-Dawley rats.

“Perinatal genistein is an endocrine disrupter and increases multiplicity of MNU-induced mammary carcinoma in rats.”

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Women are at greater risk for breast cancer if they have abnormal cytology in nipple aspirates of breast fluid.<sup>45</sup> The following study indicates that soy proteins increase breast fluid, cause epithelial hyperplasia and contribute to other abnormalities associated with increased risk of breast cancer.

**Petrakis NL. Barnes S et al.** Stimulatory influence of soy protein isolate on breast cancer secretion in pre-and postmenopausal women. *Cancer Epidemiol Biomarkers Prev*, 1996, 10, 785-794.

“Soy foods have been reported to have protective effects against premenopausal breast cancer in Asian women. No studies have been reported on potential physiological effects of dietary soy consumption on breast gland function. We evaluated the influence of the long-term ingestion of a commercial soy protein isolate on breast secretory activity. We hypothesized that the features of nipple aspirate fluid (NAF) of non-Asian women would be altered so as to resemble those previously found in Asian women. . . . Of potential concern was the cytological detection of epithelial hyperplasia in 7 of 24 women (29.2%) during the months they were consuming soy protein isolate. The findings did not support our a prior hypothesis. Instead, this pilot study indicates that

prolonged consumption of soy protein isolate has a stimulatory effect on the premenopausal female breast, characterized by increased secretion of breast fluid, the appearance of hyperplastic epithelial cells and elevated levels of plasma estradiol. These findings are suggestive of an estrogenic stimulus from the isoflavones genistein and daidzein contained in soy protein isolate. ”

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In its August 2004 letter to the FDA, Solae explained that it failed to include research led by William Helferich, M.D., at the University of Illinois, Urbana/Champaign, because “soy food was not used as a treatment” in these studies. In fact, these studies used soy protein isolate-based feeds containing increasingly high concentrations of the soy isoflavone genistein. We hold that these studies must not be ignored as they do in fact link soy protein – and especially the constituents of soy protein known as genistein – to the acceleration of breast cancer in women who have already been diagnosed with the disease.

Solae acknowledged that these studies establish the fact that soy phytoestrogens support the growth of estrogen-dependent tumors, but stated that this only occurs in the absence of endogenous estrogens. Despite the fact that most postmenopausal women show low levels of endogenous estrogen, Solae rejected the obvious conclusion that soy protein containing genistein is potentially dangerous for them. Instead, Solae chose to focus on the possibility that soy genistein can inhibit cancer growth when endogenous estrogens are present. Because women have different levels of endogenous estrogens during different phases of their life cycle, increased consumption of soy protein cannot safely be recommended to all women, much less to men and children. Furthermore, a “soy-protein-prevents-cancer” health claim would encourage many women to purchase soy isoflavone supplements even though the claim would only be made for soy protein. On this, Dr. Helferich is clear: “Our preclinical laboratory animal data suggest that caution is warranted regarding the use of soy supplements high in isoflavones for women with breast cancer, particularly if they are menopausal.”<sup>46</sup>

Solae's remarks regarding Tamoxifen also deserve comment. Solae stated that the chemical structure of Tamoxifen is "similar to that of genistein," that genistein has "no more effect" than Tamoxifen and that the FDA has approved Tamoxifen for breast cancer prevention in women who are at high risk of developing breast cancer." All this is true, but the FDA approved Tamoxifen as a *drug* and not as a food. The FDA has not recommended that the entire population male and female, adults and children be medicated with this pharmaceutical in the interest of cancer preventive. We hold that soy genistein, like Tamoxifen, may have promise as a pharmaceutical drug, not as a food, and that it should be carefully administered, monitored and recommended as such.

On June 14, 2004, Weston A. Price Foundation submitted evidence that genistein may negate the Tamoxifen effect, thus proving hazardous to women undergoing cancer treatment. To address this issue, Solae presented several studies indicating that dietary soy is synergetic with Tamoxifen. Solae stated that chemical structure of both Tamoxifen and genistein are similar to that of estrogen and that "these compounds can inhibit, have no effect, or even support the growth of estrogen dependent tumors depending on doses used and the estrogen status of a given model." In other words, both the prescription drug and the non-prescription soy isoflavone can have many possible effects, some of strong potency and none entirely predictable. Instead of proving safety, we maintain that these studies suggest that genistein should sometimes be recommended by a licensed physician to be given in conjunction with Tamoxifen as a prescription drug, with the dose carefully calculated and the patient's progress carefully monitored. We hold that it is inappropriate and irresponsible for Solae to encourage women to eat increased amounts of genistein-containing soy protein at will. Such haphazard dietary use of soy protein could prove especially hazardous to women with breast cancer. We hold that the health and very lives of these women might depend upon a clear warning label on packages of soy protein products.

### B3.2. Prostate Cancer

In its health claim petition, Solae stated that “the totality of the publicly available scientific evidence supports the substance/disease relationship that consumption of soy protein-containing foods is related to a lower risk of prostate cancer in men.” We submit that the British Committee on Toxicity (COT) is correct when it states in its “Working Draft on Phytoestrogens” that “The epidemiological data on soy intake and prostate cancer are inconsistent” and that concentrations used in animal experiments are “very high compared with the likely dietary exposure levels in humans.”

<http://www.foodstandards.gov.uk/multimedia/webpage/phyto-reportworddocs>

The following group of human and animal studies omitted from Solae’s “thorough review of the literature” show that soy foods are *not* protective against prostate cancer, are less effective than other dietary agents or have been linked to *increased* prostate cancer risk. In addition, these dietary compounds have caused undesirable side effects, including changes to the dimorphic brain region and increased IGF-1 levels. Below is a selection of the studies indicating that a warning label on soy protein products is more appropriate than a health claim.

**Doerge D, Chang H.** Inactivation of thyroid peroxidase by soy isoflavones in vitro and in vivo. *J Chromatogr B. Analyt Technol Biomed Life Sci*, 2002, 777 (1-2), 269.

Drs. Doerge and Chang review the evidence in humans and animals for anti-thyroid effects of soy and its principal isoflavones, genistein and daidzein. They note that genistein interferes with estrogen receptors in rat prostate glands which “. . . may have implications for reproductive toxicity and carcinogenesis that warrant further investigation.”

**Lephart ED, Adlercreutz H, Lund TD.** Dietary soy phytoestrogen effects on brain structure and aromatase in Long-Evans rats. *Neuroreport*. 2001, 16; 12, 16,:3451-3455.

“We found that dietary phytoestrogens: significantly decrease body and prostate weights, do not alter brain aromatase levels and significantly change during adulthood the

structure of the sexually dimorphic brain region (i.e. anteroventral periventricular nucleus; AVPV) in male, but not in female rats. Since most commercial animal diets contain significant concentrations of phytoestrogens their influence on brain structure should be considered.”

**Spentzos D, Mantzoros C et al.** Minimal effect of a low-fat/high soy diet for asymptomatic, hormonally naive prostate cancer patients. *Clin Cancer Res.* 2003 15, 9, 9, 3282-3287.

“PURPOSE: The effects of a low-fat diet or a low-fat diet with the addition of a soy supplement were investigated in a pilot Phase II study for asymptomatic, hormonally naive prostate cancer patients with rising prostate-specific antigen (PSA) levels. . . CONCLUSIONS: A low-fat diet with the subsequent addition of a soy supplement did not result in a significant decline in PSA levels. The addition of soy protein had a modest effect on TTP. A potentially undesirable effect associated with the administration of soy was an increase in IGF-I serum levels.”

**Cohen LA, Zhao Z, Pittman B, Scimeca J.** Effect of soy protein isolate and conjugated linoleic acid on the growth of Dunning R-3327-AT-1 rat prostate tumors. *Prostate.* 2003, 54, 3, 169-180.

“BACKGROUND: Epidemiologic and animal model studies suggest that consumption of soy isoflavones may be associated with reduced risk of prostate cancer (PC). In addition, animal model studies suggest that conjugated linoleic acid (CLA), a natural positional isomer of linoleic acid, inhibits tumor growth in various models, including models of PC. RESULTS: The results of this study indicate that neither an isoflavone-rich soy protein isolate (SPI), nor CLA inhibit the in vivo growth and development of prostate tumor cells when administered in the diet either singly or in combination. Moreover, at the highest concentrations SPI and CLA (i.e., 20% SPI, 1% CLA), there was a statistically significant increase in tumors volume over controls. Administration of SPI at 10% in the diet also enhanced tumor growth, whereas at 5%, SPI exerted no measurable effect. CLA administration alone had no observable effects on AT-1 tumor growth. . . CONCLUSION: These results, in an established rat model,

suggest caution in using isoflavone-rich SPI in human studies involving advanced hormone-refractory prostate cancer until further investigation of these effects are completed. “

**Probst-Hensch NM, Wang H et al.** Determinants of circulating insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations in a cohort of Singapore men and women. *Cancer Epidemiol Biomarkers Prev.* 2003, 8, 739-746.

“Variation in the circulating concentrations of the insulin-like growth factor (IGF) system has been implicated in the etiology of chronic diseases including cancer (prostate, breast, colon, and lung), heart disease, type 2 diabetes, and osteoporosis. We searched for sociodemographic, anthropometric, reproductive, lifestyle, and dietary determinants of IGF-I and insulin-like growth factor binding protein (IGFBP) -3 serum concentrations . . . Intake of soy was associated positively with IGF-I and molar ratio concentrations, but only in men. The results of this study lend additional support to the hypothesis that circulating IGF-I concentrations increase the risk of prostate, bladder, colorectal, and breast cancer.”

**Cohen LA, Zhao Z, Pittman B, Scimeca J.** Effect of soy protein isolate and conjugated linoleic acid on the growth of Dunning R-3327-AT-1 rat prostate tumors. *Prostate.* 2003, 54, 3, 169-180.

“BACKGROUND: Epidemiologic and animal model studies suggest that consumption of soy isoflavones may be associated with reduced risk of prostate cancer (PC). In addition, animal model studies suggest that conjugated linoleic acid (CLA), a natural positional isomer of linoleic acid, inhibits tumor growth in various models, including models of PC. . . .RESULTS: The results of this study indicate that neither an isoflavone-rich soy protein isolate (SPI), nor CLA inhibit the in vivo growth and development of prostate tumor cells when administered in the diet either singly or in combination. Moreover, at the highest concentrations SPI and CLA (i.e., 20% SPI, 1% CLA), there was a statistically significant increase in tumors volume over controls. Administration of SPI at 10% in the diet also enhanced tumor growth, whereas at 5%,

SPI exerted no measurable effect. CLA administration alone had no observable effects on AT-1 tumor growth. **CONCLUSION:** These results, in an established rat model, suggest caution in using isoflavone-rich SPI in human studies involving advanced hormone-refractory prostate cancer until further investigation of these effects are completed.”

**Santti** Developmental estrogenization and prostatic neoplasia. *Prostate*, 1994, 24, 2, 67-78.

“Evidence indicates that estrogen exposure during development may initiate cellular changes in the prostate which would require estrogens and/or androgens later in life for promotion of prostatic hyperplasia or neoplasia. . . The critical time for estrogen action would be during the development of prostatic tissue. We further suggest that estrogen-sensitive cells may remain in the prostate and be more responsive to estrogens alter in life or less responsive to the normal controlling mechanisms of prostate growth”

In other words, a male fetus exposed to soy phytoestrogens from his mother’s diet would be more likely to develop prostate cancer later in life.

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**Pollard M, Wolter W, Sun L.** Diet and the duration of testosterone-dependent prostate cancer in Lobund-Wistar rats. *Cancer Lett.* 2001, 173, 2, 127-131.

In its petition Solae sums this study up as follows: “Providing rats an ISP diet during age 12-24 months, the stage of spontaneous prostate tumor development, significantly reduces tumor incident compared with the controls on a soy meal diet.”

The researchers, however, conclude their abstract with this revealing statement: “Dietary soymeal found in most natural ingredient diets may promote PC tumorigenesis, but only in L-W rats.” L-W rats were developed, in the words of these researchers as “a unique model of spontaneous prostate cancer (PC)” that “shares many of its characteristics with the natural history of PC in man, including (a) inherent predisposition, high production of testosterone and aging risk factors, (b) endogenous tumorigenic mechanisms, and (c) early stage testosterone-dependent and late stage testosterone-independent tumors.”

\* \* \* \* \*

Finally, Solae has omitted discussion of the prevailing theories about why soy might be protective against the development of prostate cancer. Prostate cancer is generally thought to be dependent on exposure to male reproductive hormone. If soy confers protection, it is by altering endogenous hormone concentrations – by decreasing testosterone and androgen levels and estrogenizing men. While this theory might have valid pharmaceutical applications in cancer treatment, it seems inadvisable as a preventative treatment for the entire male population.

### B.3.3. Gastro-Intestinal Cancer

In this section Solae states that a “thorough review of these studies reveals that consumption of soyfoods is related to a lower incidence of gastro-intestinal cancer in humans.” To reach this conclusion, Solae had to omit numerous studies showing adverse effects. The British Committee on Toxicology (COT) states that epidemiological studies exploring the relationship between soy consumption and the risk of stomach and colorectal cancer have “provided inconsistent results.”

<http://www.foodstandards.gov.uk/multimedia/webpage/phytoreportworddocs>

Solae has also incorporated all negative findings regarding soy and gastrointestinal cancers into its meta-analyses. This had the effect of obscuring the conclusions of Nagata et al 2000, an important study which showed that soy protein was associated with a lowered risk of stomach cancer but also with a higher risk of death from colorectal cancer.<sup>47</sup> It hardly seems appropriate to claim benefit for a food that might prevent stomach cancer but put a person at higher risk for colon cancer.

Furthermore, Solae omitted several key studies included below that link soy protein to the development of intestinal cancers or that document precancerous damage caused by soy protein. These studies support a requirement for a warning label on soy protein products, not a health claim.

**McIntosh GH, Regester GO et al.** Dairy proteins protect against dimethylhydrazine-induced intestinal cancers in rats. *J Nutr*, 1995, 125, 809-816.

“ . . . The tumor data indicated that dietary whey protein and casein were more protective against the development of intestinal cancers in rats than were the red meat and soybean diets. No statistically significant difference was observed between the effects of casein and the effects of whey protein. In addition, no significant difference in tumor incidence or burden could be measured between the animals fed the red meat diet and those fed the soybean protein diet. . . . Our data also suggest that, like meat, soybean may not be an optimal source of protein for the gastrointestinal tract.

**Govers MJ, Lapre JA et al.** Dietary soybean protein compared with casein damages colonic epithelium and stimulates colonic epithelial proliferation in rats. *J Nutr* 1993, 123, 1709-1713.

“ . . . epithelial cell damage and proliferation of colonic epithelium (measured as in vivo incorporation of tritiated thymidine into DNA) were greater in rats fed soybean protein. The stimulation of colonic proliferation by soybean protein is consistent with the observed increase in luminal cytolytic activity and epithelial cell damage. We conclude that the stimulatory effect of soybean protein on endogenous magnesium excretion is due to a soybean protein-specific damage of colonic epithelial cells, which results in a compensatory epithelial cell hyperproliferation.”

[Cell proliferation has been identified as an early biomarker of colon cancer risk.]

Soybeans also contain antinutrients known as lectins that bind to the villi and crypt cells of the small intestine. Lectin binding contributes to cell death, a shortening of the villi, a diminished capacity for digestion and absorption, cell proliferation in the crypt

cells, interference with hormone and growth factor signaling and unfavorable population shifts among the microbial flora. All these factors contribute to intestinal cancers.<sup>48-51</sup>

Finally, Solae claims that soy protein is a high-quality, complete protein, containing all the essential amino acids. The sulfur-containing amino acid methionine, however, is so underrepresented in soy protein that it must be added to soy infant formula and to soy-based animal feeds. This deficiency makes soy protein a questionable food for colon cancer prevention in that several studies indicate that methionine has been shown to be prevent colon cancer.<sup>52,53</sup>

### APPENDIX III: SCIENTIFIC EVIDENCE – OTHER CANCERS

Solae provides summaries of a number of studies that “reflect a trend that consumption of soyfoods is related to a lower risk of cancerous diseases. However, the number of studies is limited and findings are not consistent in certain types of cancers.” We would agree that the studies are inconsistent and sometimes contradictory. However, we do not agree that the number of studies is limited, and wish to comment on the high probability that soy protein consumption contributes to thyroid and pancreatic cancers as well as to leukemia.

The American Cancer Society reports that overall thyroid cancer incidence across all ages and races is now increasing at 1.4 percent per year and that incidences rose 42.1 percent between 1975 and 1996, with the largest increases among women. Thyroid carcinoma is one of the most common cancers among US children and adolescents, with approximately 75 percent occurring to adolescents between the ages of 15 and 19. The National Cancer Institute (NCI) comments that “the preponderance of thyroid cancer in females suggest that hormonal factors may mediate disease occurrence.” “Hormonal factors” could include the phytoestrogens in soy protein products.

The following studies by FDA scientists state a strong possibility of a link between soy protein-with-isoflavones consumption and thyroid cancer risk.

**Divi RL, Chang HC, Doerge DR.** Anti-thyroid isoflavones from soybean: isolation, characterization, and mechanisms of action. *Biochem Pharmacol.* 1997. 10, 1087-96.

”The soybean has been implicated in diet-induced goiter by many studies. The extensive consumption of soy products in infant formulas and in vegetarian diets makes it essential to define the goitrogenic potential. In this report, it was observed that an acidic methanolic extract of soybeans contains compounds that inhibit thyroid peroxidase-(TPO) catalyzed reactions essential to thyroid hormone synthesis. . . . Because inhibition of thyroid hormone synthesis can induce goiter and thyroid neoplasia in rodents, delineation of anti-thyroid mechanisms for soy isoflavones may be important for extrapolating goitrogenic hazards identified in chronic rodent bioassays to humans consuming soy products.”

**Divi RL, Doerge DR Inhibition of thyroid peroxidase by dietary flavonoids.**  
*Chem Res Toxicol.* 1996, 9, 1, 16-23.

“Flavonoids are widely distributed in plant-derived foods and possess a variety of biological activities including antithyroid effects in experimental animals and humans. . . . These inhibitory mechanisms for flavonoids are consistent with the antithyroid effects observed in experimental animals and, further, predict differences in hazards for antithyroid effects in humans consuming dietary flavonoids. In vivo, suicide substrate inhibition, which could be reversed only by de novo protein synthesis, would be long-lasting. However, the effects of reversible binding inhibitors and alternate substrates would be temporary due to attenuation by metabolism and excretion. The central role of hormonal regulation in growth and proliferation of thyroid tissue suggests that chronic consumption of flavonoids,

especially suicide substrates, could play a role in the etiology of thyroid cancer.”

A substantial body of evidence connects the antinutrients known as protease inhibitors (or trypsin inhibitors) in soy to pancreatic hyperplasia, a precursor to pancreatic cancer. It may not be coincidental that pancreatic cancer recently moved up to fourth place as a cause of cancer deaths in men and women in the United States as consumption of soyfoods in this country has increased. In the 1970s and 1980s, several researchers studying protease-inhibitor damage on the pancreas noted that pancreatic cancer had then moved up to fifth place and theorized that there might be a soybean-protease inhibitor connection. The fact that this ongoing rise has occurred along with a rise in the human consumption of soybeans does not prove cause and effect. However, looking at the increase in pancreatic cancer cases alongside pertinent animal studies showing stress on the pancreas, precancerous conditions and pancreatic cancer is suggestive – and sobering.<sup>54-60</sup> Irvin E. Liener, Ph.D of the University of Minnesota, a leading expert on plant toxins and antinutrients, has warned that “Soybean trypsin inhibitors do in fact pose a potential risk to humans when soy protein is incorporated into the diet.”<sup>61</sup>

Solae also failed to open a discussion about soy protein’s link to thymus damage and immune system suppression, a possibility that further undermines any assertion that soy protein affords protection against cancer.<sup>62</sup>

Finally, Solae neglected to address the matter of uterine cancers caused prenatally by soy isoflavones, a very real risk for women such as vegans who would be likely to eat excessive amounts of soy protein during pregnancy, or the link between soy and leukemia. We quote from three of these studies below:

**Newbold RR, Banks EP et al.** Uterine adenocarcinoma in mice treated neonatally with genistein. *Cancer Res.* 2001 Jun 1;61(11):4325-8.

“The developing fetus is uniquely sensitive to perturbation with estrogenic

chemicals. The carcinogenic effect of prenatal exposure to diethylstilbestrol (DES) is the classic example. Because phytoestrogen use in nutritional and pharmaceutical applications for infants and children is increasing, we investigated the carcinogenic potential of genistein, a naturally occurring plant estrogen in soy, in an experimental animal model previously reported to result in a high incidence of uterine adenocarcinoma after neonatal DES exposure. Outbred female CD-1 mice were treated on days 1-5 with equivalent estrogenic doses of DES (0.001 mg/kg/day) or genistein (50 mg/kg/day). At 18 months, the incidence of uterine adenocarcinoma was 35% for genistein and 31% for DES. These data suggest that genistein is carcinogenic if exposure occurs during critical periods of differentiation. Thus, the use of soy-based infant formulas in the absence of medical necessity and the marketing of soy products designed to appeal to children should be closely examined.”

**Strick R, Strissel PL et al.** Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia. *Proc Natl Acad Sci USA*, 2000, 25, 97, 9, 4790-4795.

”Chromosomal translocations involving the MLL gene occur in about 80% of infant leukemia. In the search for possible agents inducing infant leukemia, we identified bioflavonoids, natural substances in food as well as in dietary supplements, that cause site-specific DNA cleavage in the MLL breakpoint cluster region (BCR) in vivo. The MLL BCR DNA cleavage was shown in primary progenitor hematopoietic cells from healthy newborns and adults as well as in cell lines; it colocalized with the MLL BCR cleavage site induced by chemotherapeutic agents, such as etoposide (VP16) and doxorubicin (Dox). Both in vivo and additional in vitro experiments demonstrated topoisomerase II (topo II) as the target of bioflavonoids similar to VP16 and Dox. Based on 20 bioflavonoids tested, we identified a common structure essential for topo II-induced DNA cleavage. Reversibility experiments demonstrated a religation of the bioflavonoid as well as the VP16-induced MLL cleavage site. Our observations support a two-stage model of cellular processing of topo II inhibitors: The first and reversible stage of topo II-induced DNA cleavage results in DNA repair, but also rarely in chromosome translocations; whereas the second, nonreversible stage leads to cell death because of an

accumulation of DNA damage. These results suggest that maternal ingestion of bioflavonoids may induce MLL breaks and potentially translocations in utero leading to infant and early childhood leukemia.”

**Editorial --** Infantile Leukemia and soybeans – a hypothesis *Leukemia*, 1999, 13, 317-320.

“Recent molecular-genetic studies have revealed that in the majority of patients with secondary leukemia induced by topoisomerase II (topo II) inhibitors and also with infantile acute leukemia (IAL), the breakpoints are clustered within scaffold attachment regions (SARS) of 3’-MLL-bcr near exon 9. Genistein, abundant in soybeans, is reported to be a potent nonintercalative topo II inhibitor. It interferes with the break-reseal reaction of topo II by stabilizing a cleavable complex, which in the presence of detergents, results in DNA strand breaks. The present study revealed that genistein induced chromatid-type aberrations in which chromatid exchanges are often observed. Genistein seems to act in a manner very similar to that of VP-16, although the latter is reported to produce both chromatid-and-chromosome-type aberrations. In view of this pharmacological similarity between genistein and VP-16, and also the similarity of breakpoint clustering regions within the MLL gene in reported cases with secondary leukemia and IAL, genistein may be largely responsible for the development of IAL.”

\* \* \* \* \*

**IN CONCLUSION:** We have provided abundant scientific evidence that consumption of soy protein/soy isoflavones can contribute to, cause and/or accelerate the growth of certain types of cancer, thus establishing the fact that a “soy-prevents-cancer” health claim would be false and misleading and so constitute a betrayal of public trust. We submit that a warning label indicating that soy protein can contribute to, cause the growth of and/or accelerate the growth of cancer would best serve the American public.

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